FUNDAMENTAL IMMUNOLOGY

SECOND EDITION

Editor

WILLIAM E. PAUL, M.D.

Laboratory of Immunology
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Raven Press New York

munosuppression has received considerable attention. Binz and Wigzell reported successful abrogation of rejection reactions in rats by treatment with anti-idiotypic reagents that they produced by immunizing with either alloantisera or mixtures of alloreactive T cells (229). These results, however, proved difficult to reproduce, possibly because the receptors involved were extremely heterogeneous. To avoid the problem of heterogeneity, other investigators have used monoclonal anti-MHC antibodies as a source of receptors against which to produce anti-idiotypic reagents (230,237). Such reagents have been shown to have profound effects on the humoral immune response to MHC antigens but have so far been unsuccessful in modifying T cell responses to the same antigens or in affecting the survival of skin grafts across similar MHC disparities (232). Based on these studies, it would appear that the anti-MHC receptors on antibodies and on T cells rarely, if ever, share idiotypic determinants. The failure to detect idiotype sharing probably reflects a difference in the allogeneic determinants recognized by B and T cells. Therefore present attempts toward modifying T cell immunity to MHC antigens by anti-idiotypes are focusing on reagents produced against T cell receptors.

Enhancement

Enhancement is defined as prolongation of graft survival by the presence of anti-graft antibody (233). This phenomenon was first described for its role in enhancing allogeneic tumor growth (234). Subsequently, Stuart and colleagues (235) and Batchelor (236) demonstrated that enhancing regimens using anti-MHC antibodies and/or soluble antigen could produce long-term tolerance for allogeneic kidney transplants (237). The simple interpretation that anti-MHC antibodies bind to the antigen and thereby block the immune response is insufficient to explain all the data. For example, tolerance following enhancement can be transferred by cells and not serum from enhanced recipients. Apparently, the administered antibody sets up a host reaction that leads to specific immunosuppression. An idiotype–anti-idiotype network would be an attractive explanation for this phenomenon. Unfortunately, the spectacular success obtained using enhancement for kidney graft survival in rats has not been observed for other grafts in other species.

Chimerism as an Approach to Tolerance

A very effective means for producing long-term tolerance in adult mice involves total-body irradiation followed by allogeneic bone marrow transplantation. If mature T cells are eliminated from the bone marrow inoculum by treatment with anti-T cell antibodies, then chimeras are produced that do not succumb to GVHD and are fully tolerant to donor-type tissue grafts (218,219). However, such animals remain relatively immunoincompetent, presumably because the new T cells that arise have matured in a thymus that is histoincompatible with the marrow elements (and therefore APCs) (238). Therefore the thymus MHC is recognized as self but the peripheral presenting cells are not of the same haplotype. Thus bone marrow transplantation accomplishes specific immunosuppression but the limitations of GVHD and/or immunoincompetence make it less than an ideal procedure.

Two approaches have recently been developed that permit the use of bone marrow transplantation as a specific immunosuppressive regimen. The first involves total lymphoid irradiation (TLI) plus bone marrow transplantation and has been studied extensively by Slavin and colleagues (221). The long bones are shielded during the radiation preparative regimen, and thus bone marrow transplantation leads to mixed chimeras rather than fully allogeneic chimeras. Animals treated this way have been shown to be both resistant to GVHD and tolerant to skin grafts from donor but not third-party animals. The second approach has been called mixed marrow reconstitution and involves total-body irradiation of recipients and reconstitution with a mixture of T-cell-depleted syngeneic and allogeneic bone marrow cells. Mixed bone marrow chimeras have been shown by Singer and colleagues to be fully immunocompetent (239), and studies by Ildstad and Sachs have shown such animals to be fully tolerant to subsequent skin grafts from the donor but not third-party strains (240). The mechanism by which both of these methods lead to specific immunosuppression, resisting both rejection of the graft and GVHD, remains under investigation (241).

Neonatal Tolerance

Another means of achieving tolerance to alloantigens is by the introduction of the foreign antigens early in ontogeny. Owen first described such an example of transplantation tolerance in cows that had shared placental circulation *in utero* (242). The phenomenon was demonstrated and studied extensively by Medawar and colleagues in rodents, in which tolerance can be induced by injection of bone marrow within several days of birth (243). Like the production of bone marrow chimeras, the achievement of tolerance in this manner probably depends on the presentation of antigen before the development of a competent T cell repertoire. Thus developing T cells treat the foreign antigen as "self." Unlike the production of adult radiation chimeras, neonatal tolerization is unlikely to have practical application in clinical transplantation. The process does, however, offer a system to study how tolerance to self antigens is achieved.

IMMUNOLOGIC ASPECTS OF CLINICAL TRANSPLANTATION

Clinical Syndromes of Graft Rejection

Hyperacute Rejection

Hyperacute rejection is said to occur when an organ suffers from rejection within minutes to hours after trans-

plantation. The phenomenon is usually visible and dramatic. Transplanted kidneys that have initially perfused well turn blue and mottled within minutes. Urine output ceases and recovery does not occur. Microscopically, organs usually show evidence of extensive vascular thrombosis without evidence of a mononuclear cell infiltrate (244).

The crucial element in hyperacute rejection is usually the presence in the recipient of antibody capable of reacting with antigens present on the vascular endothelium of the donor organ. This antibody may be directed at blood group or MHC antigens. In some instances hyperacute rejection may occur by a cell-mediated mechanism (245). Clinical aspects of importance with respect to hyperacute rejection include: (a) not all organs are equally susceptible to hyperacute rejection. For example, the kidney is very susceptible, the heart and pancreas are probably susceptible, and the liver is especially resistant to hyperacute rejection (246). (b) No form of immunosuppression is yet recognized to be effective in preventing or treating hyperacute rejection; but (c) effective preoperative cross-matching has made hyperacute rejection an unusual event.

Acute Rejection

Very few organs suffer hyperacute rejection after careful cross-matching. However, rejection episodes occurring toward the end of the first week after transplantation are common and even expected despite the use of immunosuppression from the time of transplantation. These episodes are separable from those of hyperacute rejection by the later timing of their occurrence, by the prior absence of anti-donor antibody in the recipient, and by the cellular infiltrate usually present on biopsy in the absence of vascular thrombosis. Most rejection events treated by clinicians are of this sort. Acute rejection may occur at any time after transplantation, but with decreasing frequency over the first 3 to 6 months. Such rejection may even occur much later after transplantation if immunosuppression medication is withdrawn.

Acute rejection of organ allografts is thought to be a cell-mediated event. The best clinical evidence that a rejection episode is of the acute, therefore cell-mediated, type is from the response to therapy. Acute rejection episodes are the most apt to be responsive to the available forms of increased immunosuppression including high-dose steroid therapy or anti-lymphocyte antibody therapy. Indeed the current success of monoclonal anti-T cell antibody treatment in reversing first acute rejection episodes is sufficient to call into question the diagnosis of cellular rejection if therapy is unsuccessful (124).

Another early form of allograft rejection is termed "accelerated" rejection, referring to an unusually early and unusually intense event which is nonetheless separable in time from immediate hyperacute rejection and without its universally poor outcome. Accelerated rejection occurs several days after transplantation and pathologically reveals fibrinoid necrosis of small vessels (247). It may be mediated by recipient antibody which was present in quantities too low for detection by a cross-match. Alternatively, some cases of accelerated rejection may represent cell-mediated immunity in previously sensitized recipients.

Chronic Rejection

Most organs that succumb to rejection are lost within the first 3 months after transplantation. Nonetheless, continued failure of tissue grafts due to immunologic causes may occur after the first 3 months and even after the first year. Such late rejection, especially if occurring over prolonged periods and if unresponsive to increased immunosuppression, is termed "chronic" rejection. The implication is one of a persistent, inexorable process beyond the control of medical therapy. Biopsy results may show chronic interstitial fibrosis in the kidney with mild to moderate cellular infiltrates (248). There may be vascular changes including hyalinization of vessels. It is unknown whether the process represents chronic antibody-mediated as well as cellular rejection.

The Effect of Antigen Matching on Graft Survival

Clinical Evidence

Transplantation antigens are defined by their ability to cause graft rejection and, in the absence of transplantation antigen disparities, graft rejection does not occur. Thus there can be no argument with the statement that antigen matching improves graft survival. Contrary to this simple conclusion, however, the importance of antigen matching is one of the more controversial issues in clinical transplantation. The debate is frequently confused by failure to focus on the relevant quantitative issue of how much improved, but incomplete antigen matching influences the outcome of organ transplantation under current clinical circumstances.

The evidence from transplantation of kidneys using living-related donors provides a clinical demonstration of the importance of antigen matching in subsequent graft survival. As outlined in more detail in Chapter 16, two siblings may share all of their HLA antigens (25% likelihood), half of their HLA antigens (50% likelihood), or none of their HLA antigens (25% likelihood). Identical twins share all of their transplantation antigens, but siblings are generally matched for only about half of the minor antigens, which distinguish their parents, even if they are HLA identical. Genetic recombination events within the MHC or the chance sharing of individual HLA antigens by the two parents may alter somewhat the actual number of HLA antigens shared by siblings. Table 4 shows one institution's survival rates for kidney grafts after 1 year for HLA-identical and one-haplotype matched living-related donors. Similar differences have been reported in the UCLA kidney transplant registry (249).